

## REMARKS

Entry of this Amendment and reconsideration of the subject application in view thereof are respectfully requested.

### *I. Claim Status*

Claims 1, 4-24 were pending in the application. Of these, claims 9-24 were withdrawn, and claims 1 and 4-8 were rejected. Claim 1 has been amended to clarify the invention. Support for the recitation “wherein the interaction partner binds to and modulates activity of said regulatory biomolecule” can be found in the specification, for example, at page 16, lines 34-35. No new matter is added.

### *II. Restriction/Election Requirement*

The Examiner noted at page 3 of the Office Action that “[t]he requirement is still deemed proper and is therefore made FINAL. Accordingly, claims 9-24 are withdrawn from further consideration.” Applicant respectfully requests reconsideration of the restriction requirement.

### *III. Sequence Compliance*

The Examiner noted at page 4 of the Office Action that “this application fails to comply with the requirements of 37 C.F.R. §§ 1.821(d) because the Application contains references to sequences in the specification that fail to recite a ‘SEQ ID NO.’ For example, the sequences disclosed on pages 24-27 fail to recite a SEQ ID NO and they are not presented in the sequence listing.”

As a preliminary matter, Applicant submits that the “Notice To Comply With Requirements . . .” noted in the Office Action was not attached to the Office Action. However, Applicant submits herewith amendments to the specification reciting a SEQ ID NO for each of the sequences disclosed at pages 24-27 of the specification together with an amended sequence listing presenting all of the sequences.

#### ***IV. Objection To The Specification***

The specification has been objected to because the text of the patent application contains hyperlinks and/or other forms of browser-executable code embedded in it. In response, Applicant submits herewith pertinent amendments to the specification to comply with this objection. Withdrawal of this objection is respectfully requested.

#### ***V. Claim Rejections Under 35 USC § 102***

Claims 1, 4, 5, 7 and 8 stood rejected under 35 U.S.C. § 102(b) as being anticipated by Toby, 2001, Methods, 24:201-217 (“Toby”). Applicant respectfully traverses this rejection.

Claim 1 requires, among other things, “the interaction partner of the biomolecule is encoded by the nucleic acid molecule” as recited in claim 1(a)(ii), and “assessing the expression level of the gene encoding the (poly)peptide of step a(ii) via a readout system, wherein the readout system is provided by the nucleic acid molecule encoding a reporter protein” as recited in claim 1(b)

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003). Identity of invention requires that a prior reference disclose to one of ordinary skill in the art all elements and limitations of the patent claim. *Scripps Clinic v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81 (Fed. Cir. 1986). Inherent anticipation requires that the missing descriptive material is “necessarily present,” not merely, probably or possibly present in the prior art reference. *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999). In general, a limitation or the entire claimed invention is inherent and in the public domain if it is the “natural result flowing from” the explicit disclosure of the prior art. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). To anticipate, the reference must also enable one of ordinary skill in the art to make and use the claimed invention. *In re Donohue*, 766 F.2d 531, (Fed. Cir. 1985).

Applicant respectfully submits that Toby does not teach or disclose the claimed method for monitoring the expression level of a gene in a host cell by modulating the activity of a regulatory biomolecule. Toby concerns the yeast-two-hybrid method. One skilled in the art knows that the method is used to detect protein-protein (DNA binding domain or bait and

transcription activation domain or prey) interactions. In such a system, neither the bait nor the prey can activate transcription by itself. It is the association of the bait and prey that, when co-expressed, will allow transcription of genes with regulatory sequences. The bait must bind to regulatory sequences for transcriptional activation of a reporter gene. Thus, according to the yeast-two-hybrid system of Toby, the strength of the interaction between bait and prey defines the readout obtained with the reporter system (*lacZ*). The present invention does not concern protein-protein interactions. But rather it relates to a method that determines the expression level of a gene, i.e., a method that determines a protein amount. In this method, a peptide that can modulate a regulatory biomolecule such as TetR, is used as a tag. The tag is fused to the protein of interest. The tag binds and modulates the activity of the regulatory biomolecule (the nucleic acid binding affinity of the regulatory biomolecule) which modulation subsequently causes the expression of a reporter gene located downstream of the binding site in the nucleic acid. The expression level of the reporter gene indicates the amount of the tag and thereby the amount of the tagged protein. Stated otherwise, the expression level of the reporter gene will reflect the expression pattern of the tagged protein and the amount of the tagged protein in the cell determines the readout obtained with the reporter system.

The Examiner points to Toby page 204, 2<sup>nd</sup> col., 2<sup>nd</sup> full paragraph, and Table 1, where Toby simply teaches that “. . . Interaction between bait and prey is assessed both by the transcriptional activation of colorimetric reporter, *lacZ* (Table 1), and by positive growth selection using an auxotrophic reporter gene. . .” In Table 1, Toby provides a listing of pBait and pPrey construction vectors. Thus, Toby concerns two-hybrid interactions and uses the *lacZ* and auxotrophic reporters for visualization of or selection for a two-hybrid interaction. Toby is not about a method that determines the expression level of a gene (protein amount), the expression level of which is governed by the activity of the regulatory biomolecule. The Examiner cannot establish anticipation by a simple mischaracterization of the cited reference.

The Examiner is correct in that Tobey teaches that a bait comprises a DNA binding domain. Because of this domain, the bait binds to the DNA. Tobey teaches that the bait remains bound to the DNA whether the DNA is transcriptionally inert or active. The interaction between bait and prey causes the transcriptional activation of the colorimetric reporter (*lacZ*) but that interaction be such that it must not release the bait bound to the DNA for the transcriptional activation of the reporter gene to occur. With regard to the interaction partner, the Examiner

notes the following language at page 5 of the Office Action: “interaction partner of tagged polypeptide fused to activation domain of B42”. By this language, the Examiner may be attempting to show that the Toby teaches the limitations in 1(a)(ii) and (b) but that language is insufficient to show that the limitations in 1(a)(ii) and (b) are met. First, Applicant respectfully submits, the claim requires “the interaction partner of said regulatory biomolecule,” not the interaction partner of tagged polypeptide. Further, fusing the interaction partner to the activation domain cannot result in any of the nucleic acid molecules in 1(a)(ii)(1), (2) or (3). Furthermore, the Examiner cannot establish that Toby teaches, either expressly or inherently, “assessing the expression level of the gene encoding the (poly)peptide of step a(ii) via a readout system, wherein the readout system is provided by the nucleic acid molecule encoding a reporter protein” as recited in claim 1(b).

With regard to the split two hybrid system taught by Toby (Figure 3 and legend), Applicant respectfully submits that Toby merely uses TetR as a reporter protein and there is no peptide binding to TetR. See Toby at page 216, left column, 2nd paragraph where it states:

The [split two hybrid] system is based on the two sequentially staged reporter genes. In the first one, *lexA* operator sites are incorporated upstream of the *tetR* gene . . . Interaction between LexA-fused baits and VP16 activation domain-fused preys activates the transcription of the reporter gene that encodes TetR.

Therefore, Toby fails to teach each and every limitation of claim 1, either expressly or inherently, which teaching is required for the reference to anticipate the claimed invention.

To anticipate, the cited reference must also enable one of ordinary skill in the art to make and use the claimed invention. The present application describes the claimed invention in great detail including extensive experimental data in the form of examples beginning at page 48 of the specification. This sort of enabling information is absent in Toby. One skilled in the art would know that one cannot assess the expression level of the gene encoding the (poly)peptide of step a(ii) via a readout system without this sort of enabling information and by simply following the yeast-two-hybrid methods taught by Toby. Accordingly, Toby fails to anticipate claim 1. Claims 4-8, at least by virtue of its dependency, are similarly considered by the Applicant to patentably define themselves and are novel over Toby. Reconsideration and withdrawal of this rejection are respectfully requested.

***VI. Claim Rejections Under 35 U.S.C. § 103***

Claim 5 has been rejected under 35 U.S.C. § 103(a) as being obvious over Toby, 2001, Methods, 24:201-217 (“Toby”) in view of Manfredi et al., U.S. Patent 6,828,112 (“Manfredi”). This rejection is respectfully traversed and believed to be overcome in view of the following discussion:

As a preliminary matter, Applicant respectfully believes that the obviousness rejection is directed to claim 6, which recites the “antibiotic” limitation. Accordingly, the below discussion refers to claim 6 instead of claim 5.

Claim 6 depends from claim 1. This claim further limits claim 1 from which it depends by further requiring, among other things, a protein that confers resistance to an antibiotic.

The Examiner acknowledges that Toby does not teach using a protein conferring antibiotic resistance as the reporter protein. However, the Examiner appears to be arguing that Manfredi cures the deficiencies in Toby.

The *Graham v. John Deere Co. of Kansas City*, 86 S. Ct. 684 (1966) factors control an obviousness inquiry. Those factors are: 1) “the scope and content of the prior art”; 2) the “differences between the prior art and the claims”; 3) “the level of ordinary skill in the pertinent art”; and 4) objective evidence of nonobviousness. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, at 1734 (2007) (quoting *Graham*, 383 U.S. at 17-18).

Toby is discussed above. Toby focuses on the yeast-two-hybrid systems. Indeed, Toby confirms this fact in its conclusion by stating that:

“In conclusion, although powerful, the two hybrid system is only one of a battery of different techniques that allow detection and refined measurement of protein-protein interactions.

Toby does not teach or suggest a method for monitoring the expression level of a gene in a host cell by modulating the activity of a regulatory biomolecule

Like Toby, Manfredi discloses yeast-two-hybrid systems and states the same conclusion. Manfredi does not teach or suggest the method set forth in claim 1. For example, Manfredi does not teach or suggest the limitations in 1(a)(ii)(1), (2) or (3). Further, for example, Manfredi does not teach or suggest “assessing the expression level of the gene



encoding the (poly)peptide of step a(ii) via a readout system, wherein the readout system is provided by the nucleic acid molecule encoding a reporter protein” as recited in claim 1(b). Given these fundamental differences, the Examiner has not explained why Manfredi’s teachings about a method for detecting “protein-protein interactions” which interaction leads to protein trans-splicing generating a detectable reporter could have prompted one of ordinary skill in the art to modify Manfredi in a predictable manner to arrive at the claimed invention. The Examiner has not identified a reason that would have prompted one of ordinary skill in the art in the field to transform a cell expressing a regulatory biomolecule with a nucleic acid molecule comprising an open reading frame encoding an interaction partner of the biomolecule in expressible form such that the expression level of the gene encoding the (poly)peptide of step (a) (ii) via a readout system provided by a reporter protein can be assessed

Applicant respectfully points out that the rejection on obviousness grounds cannot be sustained by mere conclusory statements (made in the second full paragraph at page 6 of the Office Action). Instead, “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F. 3d 977 (Fed. Cir. 2006). The Examiner has not provided a sufficient reason or explicit analysis of why the Manfredi reference should be modified so as to arrive at the claimed invention. Simply put, there is no suggestion in Manfredi that the proposed modification would be successful. Applicant’s method that determines specific expression patterns of proteins and thereby replaces time-consuming prior art methods of proteomics which methods are based on 2D gel electrophoresis or mass spectrometry, by a simple, quick and versatile method in which only the expression of a reporter gene has to be determined. Neither Toby nor Manfredi, either alone or in combination teaches the claimed method. Therefore, the Examiner’s rejection is believed to stand in error.

In view of the foregoing, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of claim 6 or other pending claims, under 35 U.S.C. § 103(a). Even if *prima facie* obviousness has been established, which it has not, it is urged that the cited art nonetheless fails to render the present invention obvious under a proper § 103 analysis, as the proper suggestions and motivations are lacking in the cited

reference. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.


***VII. Conclusion***

For the reasons presented above, claims 1 and 4-8 (all the claims pending in this application) are believed by Applicant to define patentable subject matter and should be passed to issue at the earliest possible time. A Notice of Allowance is requested.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the present application, the Examiner is invited to call the undersigned attorney.

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